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ALKOXY AND CYCLIC ETHER OXYGENS EXHIBIT DISPARATE CAPABILITIES FOR DIRECTING *ortho* LITHIATION

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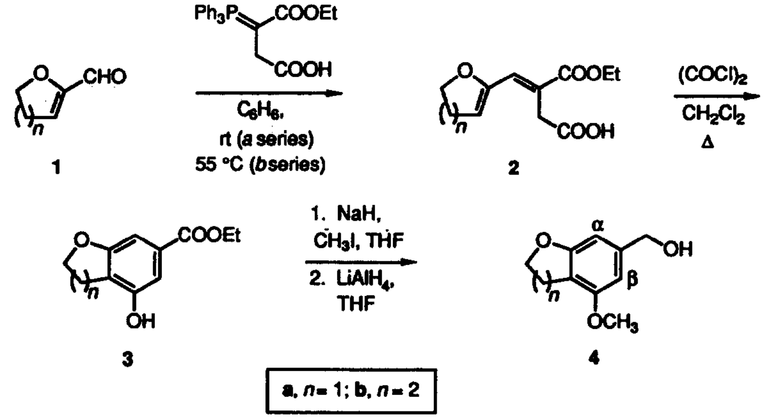
Abstract: Metalation of **4a** and **4b** with *n*-butyllithium under kinetically controlled conditions (C_6H_6, 20 °C or Et_2O, TMEDA (2 equiv), 20 °C) leads to preferred deprotonation α to the heterocyclic ring.

Heteroatom-directed ortho lithiation has matured to become a synthetic transformation of broad scope and importance to aromatic chemistry.[2] Notable for its predictive regioselectivity, efficiency, and complementarity to electrophilic Friedel-Crafts substitution, this organometalic technology has been methodically developed for application to the controlled synthesis of structurally defined, exhaustively substituted, benzenoid systems.[3] To this end, a useful ranking of substituents capable of controlling the site selectivity of carbometalation under competitive circumstances has been generated.[4] Despite this, no information apparently exists concerning the relative abilities of *identical* heteroatoms in *different* structural settings to control substitution patterns. During the development of a synthetic approach to the austalide mycotoxins, we had occasion to observe a striking example of an appreciable hierarchical difference in the directing abilities of methoxyl and dihydropyranyl ether groups. Although both types of oxygenated substituent have previously been recognized to promote kinetically enhanced ortho metalation,[5,6] they have never been allowed to vie competitively for an alkyllithium reagent. Evidence is now presented that documents the remarkable degree to which a five- or six-ring heterocyclic oxygen can dominate the deprotonation process.

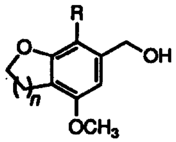
The route employed for accessing **4a** and **4b** is shown in Scheme I. For the *a* series, 2,3-dihydrofuran was metalated and reacted with DMF to give the known **1a**.[7] Condensation of this aldehyde with triphenyl(α-carbethoxy-β-carboxyethyl)phosphorane[8] provided exclusively[9] the *E*-isomer of alkylidene hemisuccinate **2a** (40%) as gauged by NOE studies at 300 MHz. Phenol **3a** was obtained spontaneously (85%) by activating **2a** with oxalyl chloride (1.4 equiv) in refluxing CH_2Cl_2. Conventional O-methylation and $LiAlH_4$ reduction furnished **4a**. 3,4-Dihydro-2*H*-pyran responded somewhat more efficiently to this series of transformations (e.g., 89% of **2b**).

Although benzyl alcohol[10] and its 3,5-dimethoxy derivative[11] are capable of ring metalation, regioselectivity considerations do not surface for reasons of symmetry. The double activation present in 3-methoxybenzyl alcohol induces successful deprotonation predominantly at C-2.[11,12] The two nonequivalent reactive sites (labeled as α and β) in **4a** and **4b** superficially appear to be closely balanced electronically for attack by a strong base. The results of lithiation studies performed with *n*-BuLi are collected in Table I. These reactions were conducted at rt either in benzene or in ether

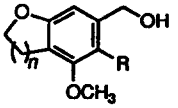
Scheme I



containing 2 equiv of TMEDA. N,N-Dimethylformamide, solid carbon dioxide, or benzaldehyde were introduced approximately 1 hour later. Strikingly, **4b** experiences α-attack exclusively (within experimental detection limits) in benzene to give **5b**-**7b**.[13] This course of events was not altered when a more bulky base (e.g., *tert*-BuLi) or electrophile (e.g., N-formylpiperidine and N-methylformanilide) was utilized. Leveling of the α/β ratio did materialize when a coordinating solvent and additive became involved. However, in no instance was **9b**-**11b** formed as the major product. The α-discrimination exhibited by **4a** is entirely parallel in direction.



5, R = CHO **7**, R = CH(OH)Ph
6, R = COOH **8**, R = CH_2Ph
(as lactone)

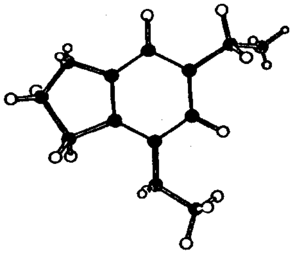


9, R = CHO **11**, R = CH(OH)Ph
10, R = COOH
(as lactone)

a, *n* = 1; **b**, *n* = 2

As demonstrated earlier both experimentally[4f] and theoretically,[14] the relative reactivity order observed for *ortho* lithiation reactions is a kinetic phenomenon associated largely with inductive contributions from the adjoining substituent. In this connection, a close parallel exists between oxygenated aromatics and vinyl ethers. The attachment of an alkoxy group to an unconjugated double bond is recognized to acidify the α proton[15] as a direct consequence of inductive stabilization.[16] Despite quite small differences in pk_a, ring size effects impact profoundly on carbanion generation, with dihydropyrans exhibiting greater kinetic acidities than dihydrofurans.[15,17] These observations reflect the importance of p-π conjunction (poorer in six-membered enol ethers than in five),[18] $\sigma^*_{C\text{-}H\alpha}$ population by oxygen *n* electrons,[16] and ring conformation (half-chair for six,[19] envelope for five[20]) on acidity and resulting ease of α-proton abstraction. The less shielded nature of the α-vinylic proton in dihydropyran (δ 6.37) relative to dihydrofuran (δ 6.22) conforms to this trend.[21]

In **4a** and **4b**, the effects are particularly dramatic because the methoxyl substituent populates mainly a ground-state conformation anti to the heterocyclic ring in order to minimize nonbonded steric interactions (see **12** and **13**; lithium cation omitted for clarity).[22] Circumstantial support for this conclusion can be derived from the ^{1}H NMR data (in C_6D_6) for **4a** (H_α, δ 6.45; H_β, δ 6.29) and **4b** (H_α, δ 6.58; H_β, δ 6.34). Although the competing transition states will surely differ from **12** and **13** in certain respects, it remains likely that the OMe oxygen will continue to be deprived of the *maximum* opportunity for *n*-electron delocalization,[18,23] with a resultant dropoff in its labilizing effect on H_β.[24]



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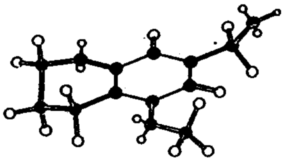

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While the nonbonded electron pairs on the methoxyl oxygen cannot readily be canted in the direction of H_β, those associated with the ring oxygens are constrained to bisecting or eclipsing H_α. Further, the reduced size of the dihydrofuran ring causes its O-C-C_α angle (127.4°) to be significantly larger than that present in **4b** (118.9°). While precoordination of oxygen to *n*-butyllithium may not be a necessary prelude to lithiation, these structural arrangements may assist in the deaggregation of this hexameric, Lewis acidic reagent[25] in benzene solution to differing degrees. As with coordination to TMEDA,[26] the consequences of possible deaggregation on rate-retarding ground-state stabilization versus kinetically-enhancing transition state activation remain difficult to dissect.[27]

Table I. Selectivity of Lithiation Reactions Involving **4a** and **4b**.

compd	reaction conditions[a]	electrophile	product yield, %	α/β ratio
4a	A	DMF	69	77:23
	B	DMF	62	78:22
4b	A	DMF	69	>97:<3
	B	DMF	65	68:32
4a	A	$CO_{2(s)}$	48[b]	79:21
	B	$CO_{2(s)}$	72[b]	81:19
4b	A	$CO_{2(s)}$	59[b]	>97:<3
	B	$CO_{2(s)}$	56[b]	72:28
4a	A	PhCHO	54	82:18
	B	PhCHO	50	83:17
4b	A	PhCHO	60	>97:<3
	B	PhCHO	49	70:30

[a] A: benzene, 20 °C, 60 min. B: ether, TMEDA (2 equiv), 20 °C, 60-90 min. [b] Based on recovered starting material.

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